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INVITED REVIEW

Myasthenic crisis

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Abstract

Myasthenic crisis (MC) is a life-threatening manifestation of myasthenia gravis (MG) defined by respiratory insufficiency that requires the use of invasive or non-invasive ventilation. This is often the result of respiratory muscle weakness but can also be due to bulbar weakness with upper airway collapse. MC occurs in approximately 15%–20% of patients with MG usually within the first 2 to 3 y of the disease course. Many crises have a specific trigger with respiratory infections being most common; however, no specific trigger is found in 30%–40% of patients. MG patients with a history of MC, severe disease, oropharyngeal weakness, muscle-specific kinase (MuSK) antibodies and thymoma appear to be at higher risk. Most episodes of MC do not occur suddenly, providing a window of opportunity for prevention. Immediate treatment is directed toward airway management and removing any identified triggers. Plasmapheresis is preferred over intravenous immune globulin as the treatments of choice for MC. The majority of patients are able to be weaned from mechanical ventilation within 1 mo and the outcomes of MC are generally favorable. The mortality rate in United States cohorts is less than 5% and mortality in MC seems to be driven by age and other medical co-morbidities. MC does not appear to affect long-term prognosis as many patients are able to eventually achieve good MG control.

KEYWORDS
mechanical ventilation, myasthenia gravis, myasthenic crisis, plasmapheresis

1 | INTRODUCTION

Myasthenic crisis (MC) is the most severe life-threatening manifestation of myasthenia gravis (MG), necessitating noninvasive and/or mechanical ventilation, supportive enteral feeding and intensive care unit (ICU) management. Historically, Samuel Wilks provided the earliest description of MC in 1887.[1] Bedlack and Sanders initially proposed that MC be defined as a clinical scenario of severe myasthenic weakness requiring intubation or delaying extubation beyond 24 h post-surgery.[2] There is, however, heterogeneity in the definition of MC. Some have designated post-operative MC as a delay in extubation beyond 48 h post-surgery; and others defined MC as the need for hospitalization to monitor respiratory status or severe dysphagia that requires enteral or parenteral nutrition.[3–6]

Abbreviations: AChR, acetylcholine receptor; ADL, activity of daily living; ARDS, acute respiratory distress syndrome; FcRn, neonatal Fc receptor; HFNC, high-flow nasal cannula; ICU, intensive care unit; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; MC, myasthenic crisis; MEP, maximal expiratory pressure; MG, myasthenia gravis; MuSK, muscle-specific kinase; NIF, negative inspiratory force; NIV, non-invasive ventilation; NMBA, neuromuscular blocking agent; PEEP, positive end-expiratory pressure; POMC, postoperative myasthenic crisis; RNS, repetitive nerve stimulation; SFEMG, single-fiber electromyography; VC, vital capacity.

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An international guideline committee proposed the following definitions: impending MC describes a rapid worsening of MG that could lead to a crisis in days to weeks; and manifest MC denotes a status of severe myasthenic weakness requiring intubation or noninvasive respiratory support, except when these measures are employed during routine postoperative management.[7]

2 | EPIDEMIOLOGY OF MC

MC occurs in approximately 15% to 20% of patients with generalized MG, typically within the first 2 to 3 y of the disease course.[8–10] The mean lead time from MG diagnosis to the first MC episode ranges from 8 to 12 mo.[10] The annual incidence of MC is approximately 2.5% among all MG patients.[11]

Elderly patients are more likely to be affected with MC. In several retrospective observational studies, the mean age at MC was approximately 60 to 70 y.[12,13] In a US claims-based study, the mean age of hospitalization with MC was 56.5 y.[14]

MC can be the first presentation of MG, occurring in 18 to 28% of MC patients.[8,11,13,15] In one large series, MC accounted for one-third of ICU admissions resulting from acute neuromuscular respiratory failure.[16] Thus, MG should be on the list of differential diagnoses for unexplained respiratory failure in patients without an established MG diagnosis.

Approximately one-third of MC survivors may experience another MC episode.[8] A portion (<5%) of myasthenic patients are refractory to treatment, and prone to suffer recurrent MC episodes in the short or long term.[11]

3 | ANATOMY, PHYSIOLOGY, AND PATHOGENESIS

MC results from weakness of the inspiratory and expiratory respiratory muscles leading to reduced respiratory volume, and/or weakness of upper airway muscles causing respiratory obstruction. In MG with acetylcholine receptor (AChR) antibodies, muscle weakness tends to initially affect the intercostal and accessory muscles then the diaphragm.[17] In patients with muscle specific kinase (MuSK) antibodies, bulbar and respiratory muscles are preferentially affected.[18]

At the initial stage of MC, microatelectasis develops, and lung volume declines progressively as respiratory muscles weaken. As the respiratory drive remains intact, rapid and shallow breathing occurs to compensate. As a result, arterial blood gases at the early stage of MC may show a respiratory alkalosis, a reduced PCO2, and a normal PO2. As the respiratory muscle weakness progresses, PCO2 may normalize, which signifies a failing respiratory system, and is typically followed by hypercapnia with respiratory acidosis (hypercapnic respiratory failure). Due to the fatigable nature of MG, respiratory muscles may suddenly wear out, precipitating a respiratory collapse, and profound hypoxemia ensues. In MG patients with chronic respiratory insufficiency, significant bicarbonate elevation may compensate for respiratory acidosis.

TABLE 1 Common triggers of myasthenic crisis

Infection including bronchitis, pneumonia, and sepsis
Aspiration pneumonitis
Reduction of immunotherapy, under-treatment, or medication nonadherence
Surgery or trauma
Pregnancy/postpartum
Medications (most frequent triggering medications):
Corticosteroid
Antibiotics (e.g., aminoglycosides, macrolides, and quinolones)
Intravenous magnesium
D-penicillamine
Botulinum toxin
Immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab, ipilimumab)
Vaccination
Emotional distress
No obvious precipitant

Oropharyngeal bulbar weakness in MC may result in upper airway collapse and obstruction along with inability to manage secretions, which often leads to aspiration and hypoxic respiratory failure. Upper airway collapse is often less well-appreciated than respiratory muscle weakness. In this clinical setting, vital capacity (VC) and negative inspiratory force (NIF), which both reflect diaphragm strength, may be deceptively normal, and the inspiratory portion of the flow-volume loop becomes abnormally flattened.

The molecular mechanisms underlying MC remain poorly understood. Mean AChR antibody concentrations are higher in patients with MC when compared to patients with mild disease.[19] At times, a significant elevation of AChR antibody titer over baseline can be associated with the occurrence of MC.[20] Prior studies of intercostal muscles in MC patients revealed widespread destruction of the postjunctional folds, implying a prominent role of complement activation at the neuromuscular junction.[21] The successful usage of eculizumab in a number of MC patients also suggests a significant role of complement activation in MC.[22–26] Finally, data suggest that certain inflammatory and regulatory cytokines are preferentially activated in MC.[27] There is an essential need for further research on the molecular mechanisms of MC.

4 | TRIGGERS, PREDICTORS, AND PREVENTION OF MC

Table 1 displays a list of the commonly encountered triggers for MC. Various types of acute infections serve as the most common class of triggers.[9,11,13] Infections are associated with 30% to 50% of MC, with the most prevalent being bacterial or viral upper respiratory infection, bronchitis, and pneumonia. Another important contributory factor is medication change, which includes initiation of medications

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that could exacerbate MG or suboptimal MG treatment due to tapering of immunotherapy or medication nonadherence. Up to 42% of MG patients administered 40–80 mg of prednisone experienced a transient worsening, and those who are older, have bulbar symptoms, or have more severe MG are more likely to experience an exacerbation.[28] The use of immune checkpoint inhibitors has led to de novo or exacerbation of prior MG in approximately 1% to 2% of patients. In many such patients, symptoms of MG are often severe, coexisting with myositis and myocarditis.[29] However, in up to 30% to 40% of MC cases, no obvious trigger can be identified.[13,30]

Risk factors for MC include previous MC, oropharyngeal weakness, severe MG symptoms, MuSK antibody positivity, or thymoma.[8,12,18,31] A large series identified thymoma in about one-third of MC patients.[12] On the other hand, achieving minimal manifestations on the MG Foundation of America Post-intervention Status at 12 mo after initial MG diagnosis indicates a low risk of future MC.[6,32]

In rare patients, MC may develop rapidly. However, most MC episodes occur with warning signs, allowing opportunities for intervention and MC prevention. In one study, 76% of MCs were preceded by increasing generalized weakness, 19% by deteriorating bulbar weakness, and 5% by worsening respiratory function. From the onset of myasthenic exacerbation to intubation, the interval was 1 to 3 days in 68%, 4 to 7 in 22%, and 14 to 21 in 10% of patients.[11] It is essential to identify and eliminate factors that have triggered MG exacerbation. Plasmapheresis or intravenous immunoglobulin (IVIG) can be used to improve strength in most MG patients as an effort to prevent MC from occurring.[13,31]

4.1 | Predictors and prevention of postoperative MC

Notable preoperative risk factors for postoperative MC (POMC) include history of prior crisis, low VC, preoperative bulbar symptoms, abnormal facial nerve repetitive nerve stimulation (RNS), and high AChR binding antibody level.[4,5,33–36] Operative risk factors for POMC include intraoperative blood loss (>1000 mL), long operation time, trans-sternal thymectomy as compared video-assisted thoracoscopic surgery, and presence of thymoma.[5,33,37] The main postoperative risk factor for POMC is postoperative pneumonia.[38]

IVIG has been used to optimize myasthenic patients prior to thymectomy, though the time to maximal response is somewhat variable, ranging from 3 to 19 days.[39] However, postoperative MC does not occur in well-controlled MG patients. Preoperative IVIG for MC prevention is not justified when quantitative MG score is less than 8 or VC is more than 70% of predicted.[40] In qualified patients who may have high risk of POMC, preoperative plasmapheresis reduces MC frequency and shortens ICU stay.[31,41] We recommend three plasmapheresis treatments in patients who need preoperative optimization. The last plasmapheresis should ideally be performed 48 h preoperatively to allow for both repletion of coagulation factors and hemodynamic stability.

Neuromuscular blocking agents (NMBAs) such as rocuronium and vecuronium (non-depolarizing agents) are often used in assisting intubation. The dose should be reduced to half that used in non-myasthenic patients.[42] Use of agents with a shorter half-life such as mivacurium should be considered.[43] Succinylcholine, a depolarizing paralytic, may not be effective due to the reduced number of post-synaptic AChRs. Sugammadex could result in a significant reduction of post-thymectomy crisis incidence by encapsulating NMBAs and reducing their action.[44] Train-of-four monitoring is recommended to oversee the degree of NMBA reversal. Azathioprine inhibits the effects of non-depolarizing NMBAs necessitating the use of higher doses operatively, so in these patients, sugammadex may be especially useful.[45]

5 | CLINICAL MANIFESTATION AND EVALUATION OF MC

The signs of MC should be sought and monitored in all myasthenic patients with significant limb weakness even when they do not note dyspnea. MG patients with significant bulbar weakness may present with limited limb and respiratory weakness, but can evolve quickly to MC due to collapse of the upper airway and/or aspiration. Conversely, some patients may present with respiratory insufficiency out of proportion to limb or bulbar weakness. In rare cases of MC, respiratory failure is the only clinically overt manifestation.[46,47]

On neurological examination, special attention should focus on the presence of ocular, orofacial, bulbar, neck, and respiratory muscle weakness. Ophthalmoparesis and ptosis are frequently seen in MC. Facial weakness may result in difficulty holding air within their cheeks along with a "myasthenic snarl" upon smiling. Jaw closure is often incomplete after chewing. Some patients place one hand beneath their chin for jaw closure. Bulbar weakness could lead to hypernasal dysarthria, hoarse speech, or dysphagia with nasal regurgitation. The presence of a weak cough reflects significant expiratory muscle weakness. Rarely stridor and vocal cord paralysis can be the main presenting feature of MC.[48,49] Tongue weakness may be assessed with protrusion of the tongue into each cheek. Evaluation for neck flexion weakness is helpful as it often correlates better with diaphragmatic strength than limb weakness.

The most reliable sign of impending respiratory failure is the presence of a paradoxical breathing pattern (i.e., inward rather than outward movement of the abdomen with each inspiration), with shallow chest expansion due to diaphragm muscle weakness.[50] The use of accessory muscles (sternocleidomastoid, scalenes, intercostals, and abdominal muscles) can often be visualized, but palpation of these muscles may make this more apparent. At times, generalized weakness and hypercapnia mask respiratory distress. Attention must be paid to respiratory rate, heart rate, difficulty with phonation, or neck weakness, all of which can signify impending respiratory failure.

The single breath test is a useful bedside measurement of respiratory function that correlates with VC and NIF. The patient is asked to take one breath in then count aloud at approximately two counts per

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second before requiring another inspiration. Ability to count to 30 with one breath correlates with adequate pulmonary function, and counting to 20 or less indicates significant inspiratory muscle weakness. One count approximately equals to 116 mL of actual VC at the speed of two counts per second.[51] Swallowing evaluation can be achieved by asking the patient to sip 3 ounces of water and then observing for coughing or choking.

Lung examination and chest X-ray may reveal findings of atelectasis, aspiration, pneumonia, or pulmonary edema. Bedside spirometry can be performed to measure VC, NIF, and maximal expiratory pressure (MEP). VC and NIF reflect the strength of inspiratory muscles, while MEP measurements correlate to the strength of expiratory muscles. NIF and MEP measurements may represent more sensitive indices of respiratory muscle function in myasthenic patients compared to VC, and a decline in MEP by 30% indicates a high risk of needing non-invasive or invasive respiratory support. By contrast, patients with VC >20 mL/kg, MEP >40 cm H_2O, or a NIF is better than −40 cm H_2O are at low risk.[52] Another useful measure of diaphragmatic weakness is a fall in VC in the supine position when compared to a seated VC.[53]

Serially trended VC, NIF, and MEP measurements are customarily used to monitor respiratory status in impending MC, although there are notable limitations. When there is significant bulbar weakness, reliable measurements may be hampered by difficulty sealing patient's lips around the mouthpiece or inability to seal the nasopharynx. In addition, measurements may not reliably predict respiratory failure in MG, due to the fluctuating nature of weakness.[54] Therefore, the decision to intubate should always be clinically based.

6 | DIAGNOSIS AND DIFFERENTIAL DIAGNOSES OF CRISIS

The majority of patients in MC carry an established diagnosis of MG. However, respiratory failure in a patient with known MG does not necessarily indicate MC. Non-myasthenic causes of respiratory dysfunction, such as pulmonary embolism, heart failure, acute respiratory distress syndrome (ARDS), or other pulmonary etiologies should be considered in the appropriate setting. Metabolic and electrolyte abnormalities or anemia can result in significant weakness, and assessment of serum electrolytes and thyroid function is recommended. Arterial or venous blood gases are helpful in the evaluation of chronic obstructive pulmonary disease or pulmonary embolism.

As discussed previously, crisis can be the first presentation of undiagnosed myasthenic patients. When such patients are encountered, differential diagnoses often include Guillain-Barre syndrome, botulism, Lambert-Eaton myasthenic syndrome, motor neuron disease, autoimmune or inflammatory myopathy, tick paralysis, and brain stem ischemia. A clinical diagnosis of MG and MC may be supported by serum antibody measurement, RNS and single-fiber electromyography (SFEMG) testing. Antibody testing for MC usually entails AChR and MuSK antibodies although treatment should not be delayed due to a pending antibody result. Low-density lipoprotein receptor-related protein 4 antibody is not indicated for MC workup due to a lack of association.[55] Edrophonium testing is no longer available in the United States.

In MC, slow-rate (ie, 2 to 3 Hz) RNS testing showing a decrement of 8% to 10% between the first and third or fourth stimuli is supportive of a MG diagnosis with a sensitivity of about 85%, especially if proximal nerves are evaluated.[56] RNS of the phrenic nerve could be assessed if other nerves are normal but this may not be practical due to technical issues.[57] SFEMG has the highest sensitivity (>90%), but is technically challenging in an ICU setting. SFEMG can be used if RNS is unremarkable and the suspicion of MG remains high.

TABLE 2 Essentials of intensive care unit (ICU) management of myasthenic crisis

Aseptic and soft suctioning
Aggressive respiratory therapy including intermittent positive pressure breathing, sigh exercise, cough augmentation, and chest physiotherapy
Bronchodilator usage (inhaled ipratropium bromide preferred due to less bronchial secretions)
Humidification of inspired gas to thin secretions.
Early placement of feeding tubes and maintenance of caloric intake at approximately 25 to 35 cal/kg, low carbohydrate feeds to reduce hypercarbia
Maintenance of electrolyte (potassium, magnesium, and phosphate) balance. Avoidance of overcorrecting hypomagnesemia.
Treatment of anemia. Transfuse when hematocrit values are under 30%.
Prophylaxis of deep-vein thrombosis prophylaxis with compression device and/or heparinoids
Hemodynamic stability and continuous cardiac monitoring
Aggressive treatment of fever and infection with effective antibiotic therapy
Optimal pain management and gentle usage of opioids

7 | MC MANAGEMENT

All myasthenic patients with questionable respiratory status should be admitted to ICU. MG activity of daily living (ADL) scale is a simple summation score of myasthenic symptoms reflecting disease severity, and an ADL score of >18 accurately predicted the need for ICU management with a sensitivity of 75% and a specificity of 78%.[58] MG exacerbations triggered by infections are more likely to require ICU admission. Management for MC and impending MC should be carried out by physicians who are experienced in the management of MG, respiratory failure, infection, and fluid/electrolyte balance (Table 2). In the absence of a neurointensivist, a team of neurologists and critical care specialists is required. A neurologist and/or a neuromuscular specialist, who ultimately provides the patient's care outside the inpatient setting, should actively participate in the management of MC. The goals of care in MC are outlined in Table 3.

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TABLE 3 Goals of care in myasthenic crisis

Immediate management of airway, respiratory and circulatory support
Confirmation of the diagnoses of myasthenia gravis and myasthenic crisis
Evaluation and treatment of acute respiratory failure
Identification and elimination of potential precipitating factors
Initiation and adjustment of immunomodulatory treatment
Prevention and treatment of complications.

7.1 | Respiratory management

7.1.1 | Intubation

Early intubation and mechanical ventilation are perhaps the most important steps in the management of MC, and emergency intubation should be avoided. Indications for intubation typically include one of the following: (1) signs of respiratory distress with increasing tachypnea and declining lung volume; (2) severe bulbar dysfunction, weak cough, and difficulty to clear secretions; (3) progressive hypercarbia on blood gas measurement; and (4) chest X-ray showing significant atelectasis and aspiration. If doubt exists, it is recommended to intubate and ventilate immediately.

When there is a suspicion for MC, the patient's vital signs, VC, NIF, and MEP as well as patient's appearance, clinical status, and their trajectory should be frequently assessed. Worsening trends in these measurements should prompt early intubation.[30] Due to the fluctuating nature of weakness in MG, no single parameter can be used to precisely predict the need for ventilatory support. Oxygen saturation and arterial blood gas measurements are generally not considered sensitive enough to be used in isolation in assisting decisions on intubation.[30] The 20/30/40 rule (VC < 20 mL/kg; NIF worse than −30 cm H_2O; and MEP < 40 cm H_2O) is a helpful tool to guide decisions regarding intubation. However, none of these threshold values have been established through high-quality prospective studies, and MG patients may precipitously develop respiratory failure before a downward trend is noted in any of these parameters. Some experts argue that VC of less than 15 mL/kg, tidal volume of less than 4 to 5 mL/kg, NIF worse than −20 cm H_2O, or MEP of less than 40 cm H_2O indicates a need for intubation.[50,59] The predictive value of both VC and NIF for intubation appears superior compared to either alone.[54] However, it is important to note that the decision to intubate is always a clinical one, rather than relying solely on measured parameters.

7.1.2 | Mechanical ventilation settings

Once mechanical ventilation commences, an assisted ventilatory setting with full mechanical support is recommended initially. Initial setting may include a tidal volume of 6 to 10 mL/kg of ideal body weight, and a pressure support setting of 5 to 15 cm H_2O. The adequacy of ventilatory support is determined by the patient's comfort and elimination of CO_2 retention. FiO_2 can be adjusted to achieve a SaO_2 > 92% or PaO_2 > 70 mmHg. In patients with chronic hypercarbia and normal pH, $PaCO_2$ should be kept above 45 mmHg or around the baseline to avoid alkalosis and bicarbonate wasting. Ultimately, the degree of ventilatory support and settings are individualized and adjusted based on clinical/respiratory status. The inspired humidity should be kept between 60% and 90%, depending on the amount of secretions. Regular checks of cuff pressure, endotracheal tube placement, and blood gases are recommended, which is not different from non-MG patients.[59]

7.1.3 | Extubation and tracheostomy

Weaning from mechanical ventilation begins when the patient is alert, hemodynamically stable, and free of triggers for MC. Weaning should be considered when there has been clinical improvement with an adequate VC (>15 mL/kg). Weaning should not be attempted prior to initiation of IVIG or plasmapheresis, unless such treatments are contraindicated. The patient should have no major pulmonary compromises (atelectasis, plural effusion, pneumonia, ARDS) or excessive secretions. Current recommendations about mechanical ventilation weaning emphasize the daily determination of simple criteria such as a satisfactory oxygenation, PaO_2/FiO_2 of being ≥200, positive end-expiratory pressure (PEEP) of being ≤8 cm H_2O, alert level of consciousness, and ability to cough effectively.

The weaning trial should start early in the day, with the initial goal of spontaneous breathing trials to eliminate mandatory ventilation, followed by a gradual reduction of the amount of pressure support. The trial should end if patients develop fatigue, tachypnea, tachycardia or agitation, and patients should be rested again on assisted mechanical ventilation settings.[59] After extubation, a period of close observation for 48 h in the ICU or a step-down unit prior to transfer to the general floor is recommended.

Low secretion volume, comfort with T-piece or spontaneous breathing trials, good neck flexor strength, and absence of significant pulmonary complication are good predictors of successful extubation. Predictors of extubation failure include age > 50 y, history of prior MC, pulmonary complications (atelectasis, pneumonia), long intubation duration, and low VC at time of extubation.[13,60,61] In several studies, atelectasis occurs in all patients requiring re-intubation.[60,61] Pulmonary function tests can be used as ancillary information to predict extubation success. However, intubated myasthenic patients with significant residual bulbar weakness may exhibit favorable respiratory parameters (i.e., VC, NIF, and MEP) but may show significant upper airway dysfunction when the stenting effect of the tracheal tube is removed. The clinical assessment of surrogate bulbar muscles (such as neck flexors) is, therefore, as important as the assessment of respiratory indices in myasthenic patients pending extubation.

Approximately 20% to 40% of patients fail extubation, leading to re-intubation.[12,13,60,61] Re-intubation significantly prolongs ICU and hospital stays. A tracheostomy should be considered for patients

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requiring more than 2 wk of mechanical ventilation. Tracheostomy placement ranges from 14% to 40% in MC.[12,61] One rare condition that often requires tracheostomy is severe upper airway obstruction due to bilateral vocal cord paralysis.

7.1.4 | Use of non-invasive ventilation

Non-invasive ventilation (NIV) can be helpful in patients prior to intubation and post extubation. In patients without overt hypercapnia, a bi-level positive airway pressure trial may be attempted prior to intubation. The use of inspiratory positive pressure helps overcome upper airway resistance, and the expiratory positive pressure opens the upper airway and prevents alveolar collapse. Overall, the initial use of NIV is associated with a shorter duration of ventilatory support and ICU stay.[13] Rabinstein and Wijdicks reviewed their experience using NIV in 11 episodes of MC in nine patients. NIV prevented intubation in 7 of them.[50] In other studies, NIV failure and subsequent intubation were as high as 37.7%.[15] Hypercapnia (PaCO2 > 50 mmHg), pneumonia, and older age predict NIV failure.[13,15,50] For NIV to be successful, it is important to have an experienced respiratory therapist help find the ideal fit for a particular patient among the various models of oronasal masks available.

NIV may also be helpful for avoiding re-intubation in myasthenic patients following extubation.[62] In patients who are doing well after extubation but still weak, it is reasonable to put the patient on NIV overnight to prevent the occurrence of ventilation failure during sleep.

Another NIV strategy is high-flow nasal cannula (HFNC), which is often used for hypoxic respiratory failure together with small amount of PEEP. As this modality is safe and comfortable for patients, HFNC can be considered for those with mild–moderate respiratory failure with hypoxemia to delay intubation or avoid reintubation, and has been used successfully in a case of MC.[63]

However, NIV provides little support to the respiratory muscles, and therefore, is not ideal for patients with respiratory muscle fatigue. NIV will likely fail in myasthenic patients who decline rapidly with significant respiratory compromise. In patients who are initially managed with NIV, intubation and mechanical ventilation should be initiated if the patient has continued or worsening shortness of breath, increased work of breathing, tachypnea, or hypercapnia (and less frequently hypoxemia).

7.2 | Disease modifying treatment

7.2.1 | IVIG and plasmapheresis

The standard dose of IVIG is 2 g per kilogram, administered over a period of 2 to 5 days. Plasmapheresis is commonly given in 5 sessions over a period of 7 to 10 days, typically exchanging 1.0 to1.5 plasma volumes (40–60 mL/kg) per session. Patients with severe MG including MC could respond well to as few as 2 sessions of plasmapheresis.[64] A randomized clinical trial of daily versus alternate day plasmapheresis (for approximately 5 sessions on average) in severe MG found no superiority of one over the other in terms of disease improvement and complication occurrence.[65]

The use of IVIG or plasmapheresis, which should be considered as first-line therapies, results in improvement in approximately 70% of myasthenic patients with severe weakness.[11,64,66–70] Improvement is usually evident by the fourth or fifth day of IVIG treatment or by the second or third plasmapheresis session, and generally lasts for weeks. AChR antibody may rebound following plasmapheresis if other maintenance immunosuppression is not initiated.[20,71]

Table 4 lists a few notable studies on the efficacy of IVIG and/or plasmapheresis in MC. While limited data seemingly indicated that plasmapheresis and IVIG are comparable in terms of efficacy, several studies have suggested that plasmapheresis led to faster and more noticeable clinical improvement and shorter ICU stay.[65,67,72,73] Stricker et al described four MC patients who failed to improve with IVIG but all responded quickly to plasmapheresis that was subsequently initiated within 48 h following the last IVIG infusion.[74] Based on the literature review and our own experience, we recommend that plasmapheresis be used as a first-line therapy in all MC patients, unless clear contraindications exist. Treatment of MC with plasmapheresis has proven to lead to fast and predictable recovery. Side effects and availability are less of a factor when working with experienced ICU and plasmapheresis teams.

If there is insufficient response to the initial treatment, plasmapheresis can be given after IVIG, and IVIG can be administered after plasmapheresis.[68,74,75] IVIG and plasmapheresis were more likely to be combined sequentially if the duration of MC and ICU stay were extended.[13] Although subsequent use of plasmapheresis after IVIG might result in removal of administered IVIG, this is usually done when there has been insufficient response to IVIG, and therefore is of little concern. As noted previously the maximal effect of IVIG may by delayed; thus, if IVIG is administered first, it may be reasonable to wait 5 to 7 days after IVIG is completed to allow for a response before pursuing plasmapheresis.[39]

7.2.2 | Corticosteroids

For patients who have not received corticosteroids, many experts defer initiating these until the patient begins to respond to plasmapheresis or IVIG due to concerns for steroid induced exacerbation. Some clinicians prefer to start corticosteroids when the patient is still intubated, so that any early exacerbation can be appropriately managed. Moderate to high doses of prednisone can be initiated in patients who are intubated or have improved significantly following plasmapheresis or IVIG; otherwise the dose can be increased in a stepwise fashion, as tolerated by the patient. Patients coming out of MC should be carefully observed for worsening weakness in an inpatient setting for several days following corticosteroid initiation.

If the patient was previously treated with corticosteroids, the same dosage can be continued initially. If clinically indicated, patients

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TABLE 4 A list of studies on the treatment of myasthenic crisis

Study	Design	MG severity and no. of patients	Treatment	Primary outcome	Result
Gajdos et al 1997	RCT	MG exacerbation including crisis ($N = 87$)	Plasmapheresis: ≈ 3 exchange sessions IVIG at 1.2 gm/kg IVIG at 2.0 gm/kg	Myasthenic muscle score at day 15	No difference
Qureshi et al 1999	Retrospective	Myasthenic crisis ($N = 54$)	Plasmapheresis: 3 to 6 sessions IVIG at 2.0 gm/kg	Myasthenia severity score at 7 days, ventilation status at 2 wk, functional outcome at 1 mo	plasmapheresis better than IVIG in all outcomes, but higher complication rate
Trikha et al 2007	RCT	Severe MG including crisis ($N = 33$)	Plasmapheresis daily or on alternative days	Myasthenia gravis disease score, duration of ventilation, removal of nasogastric tube, total hospital stay	No difference except a strong trend of shorter hospital stay for the daily plasmapheresis group
Wang et al 2022	Prospective observational cohort	Myasthenic crisis ($N = 40$)	Plasmapheresis: 5 sessions IVIG at 2.0 gm/kg	QMG, ADL, MMT score at 1 wk, 1 mo and 2 mo off ventilation, duration of ICU stay	Plasmapheresis resulted early improvement and shorter ICU stay. Plasmapheresis and IVIG efficacy comparable after 1 mo.

Abbreviations: ADL, activity of daily living; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MMT, manual muscle testing; QMG, quantitative myasthenia gravis score; RCT, randomized controlled trial.

on lower dose prednisone should have their daily dose increased by at least 20 mg when improved with plasmapheresis or IVIG.

It is important to have in mind that corticosteroids can increase the risk of critical illness myopathy. If patients have a significant infection, corticosteroid treatment should be delayed until the infection is under control. Patients with poorly controlled diabetes or osteoporosis are not good candidates for corticosteroids.

7.2.3 | Corticosteroid-sparing agents

Other immunosuppressive medications such as azathioprine, mycophenolate mofoetil, tacrolimus, methotrexate, and cyclosporine are not useful during MC principally due to their delayed onset of action. They may be used in place of corticosteroids; however, when the latter is contraindicated. At times, these agents are used together with corticosteroids in the beginning period. Initiation of such a therapy will need to take into consideration the patient's comorbidities, medication side effects and cost, and the neuromuscular specialist's preference, and is ideally considered when acute ICU management is ended or in the outpatient setting.

7.2.4 | Potential newer therapies for MC

The newly approved complement inhibitor and the neonatal Fc receptor (FcRn) antagonist therapies exhibit relatively rapid onset of action and may have a role in the treatment of MC especially for those who failed to respond to IVIG/plasmapheresis. So far eculizumab has been used in 13 patients with MC who did not respond to IVIG, plasmapheresis or both, most being AChR antibody positive. In all 13 patients, rapid and sustained improvements were observed, usually occurring within 10 days of the first eculizumab dose. In most patients, invasive and non-invasive ventilation were discontinued, while no significant side effects were observed.[22–26] Further large-scale studies are needed.

FcRn plays a central role in immunoglobulin G (IgG) homeostasis by rescuing IgGs from lysosomal degradation. By binding to the FcRn, efgartigimod interrupts this IgG recycling process and lowers the levels of IgG including AChR antibodies in the blood. Efgartigimod may serve as a rescue therapy for patients in MC as an alternative to plasmapheresis, thus "medical plasmapheresis". Its onset of action may not be as fast as traditional plasmapheresis, but improvement can still be seen within the first 1 to 2 wk. Theoretically, it can be considered in patients with contraindications to plasmapheresis like hemodynamic instability, or patients not responding to traditional rescue therapies.[76]

Last, anti-CD 20 antibodies such as rituximab have been used in the treatment of long-lasting MC after failing initial treatment of IVIG or plasmapheresis, with mixed results.[24,25,77,78] Limited case descriptions suggest that its usage could lead to steady improvement and hasten the weaning from ventilator.[77,78] However, whether the observed efficacy can be attributed to the use of rituximab in this clinical situation is unclear.

7.3 | Pyridostigmine

Pyridostigmine should be discontinued in patients intubated for MC. Its potential small benefit is outweighed by the risk of promoting

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secretion and mucus plugging. The usage of pyridostigmine also makes it difficult to assess responses to other therapies. A drug holiday can sometimes augment response to pyridostigmine. Pyridostigmine can be restarted prior to weaning mechanical ventilation in patients recovering from MC. Intravenous pyridostigmine infusion at 1 to 2 mg/h has been given to MC patients with some success.[11,30] Each milligram of intravenous pyridostigmine is equivalent to 30 mg orally. Significant, sometimes fatal, cardiac arrhythmias are a serious concern, therefore the use of intravenous pyridostigmine is discouraged.

For practical purposes, cholinergic crisis may occur in the setting of MC. However, cholinergic crisis is exceedingly rare in contemporary series of MC.[12,35] Differentiating cholinergic crisis from MC via the response to intravenous edrophonium or neostigmine is no longer necessary.[7]

8 | SPECIAL CIRCUMSTANCES

8.1 | Pregnancy

The peak incidence of MG in women is typically between the ages of 20–40 y old, which overlaps with childbearing years.[79] MG can have an unpredictable course throughout pregnancy, but exacerbations are more likely to occur in the first trimester and during the post-partum period.[80] Several treatments used for long-term disease control, like methotrexate and mycophenolate mofoetil, are contraindicated during pregnancy. Cessation of immunosuppressive medications, and the physiologic stress of labor and delivery could all serve as potential triggers for MC. Pregnant women may also be exposed to medications that could exacerbate MG or lead to MC such as intravenous magnesium for the treatment of preeclampsia or antibiotics like fluoroquinolones to treat urinary tract infections.

Overall MC occurs in 6.4% of women with MG during pregnancy and 8.2% in the post-partum period.[81] Death from MC in this clinical context is exceptionally rare.[82] Both IVIG and plasmapheresis can be used in pregnancy for MC. When plasmapheresis is considered in pregnancy, large fluid shifts and intravascular volume depletion should be carefully avoided as these could negatively affect placental perfusion. Hypercoagulable status associated with pregnancy could be exacerbated by IVIG and/or plasmapheresis so vigilance for signs or symptoms of venous thrombosis is essential.

8.2 | SARS-CoV-2 infection

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus causative of the coronavirus disease 2019 (COVID-19) pandemic is a known precipitant of MC, and patients with MG may have an increased risk for hospitalization and death from COVID-19.[83] Additionally, COVID-19 vaccination may not confer as much protection in MG patients treated with immunosuppressive drugs, especially B-cell depleting agents.[84]

During the early phases of the pandemic, data from a physician reported registry suggested that 40% of MG patients infected with SARS-CoV-2 required IVIG or plasmapheresis for worsening MG or crisis. The mortality rate in these patients was also high at 24%.[85] These numbers were artificially inflated as registry data may be biased toward reporting poor outcomes. Large-scale retrospective studies utilizing electronic health records suggest that the risk of exacerbation/crisis may be a low as 5.6% and mortality rates are closer to 6.8% to 10.6%.[83,86] It should be noted that it may be extremely difficult to differentiate MC crisis causing respiratory insufficiency and/or death from the pulmonary complications of COVID-19. The recent evolution of SARS-COV-2 virus and the less severe presentation of COVID-19 infection will likely result in even lower risks of MC and mortality in MG patients.

For MC treatment in the context of COVID-19 infection, IVIG may confer added benefit for COVID-19 as IVIG may contain SARs-CoV-2 neutralizing antibodies.[87] One patient was treated successfully with eculizumab for MC in the context of COVID-19 infection.[24] Due to use of immunosuppressive drugs, MG patients with COVID-19 are frequently candidates for anti-viral therapy to prevent disease progression.[88] It is unknown currently if anti-viral treatments confer any protection from MG exacerbation or MC.

8.3 | Thymoma and thymectomy

Thymectomy is another important option for selected myasthenic patients, but the efficacy of thymectomy is delayed. As a result, thymectomy is rarely indicated during MC. In rare cases, there is an urgent need to remove thymoma due to potential cardiopulmonary complications and risks of metastases. In these patients, a thymomectomy can be performed when the patient is hemodynamically stable while remaining intubated. Ideally, it should be done after a course of IVIG or plasmapheresis has been administered to minimize weakness.

9 | PROGNOSIS, COMPLICATIONS, AND MORTALITY

The median duration of hospitalization for MC is about 17 to 35 days, half of which is spent in the ICU.[12,13,89] In one study, about 25% of patients were extubated by hospital day 7, 50% by hospital day 13, and 75% by hospital day 31.[12] The median duration of respiratory support was 6 days in another study.[89] Risk factors for prolonged intubation include age over 50 y, pre-intubation serum bicarbonate levels above 30 mg/dL, and maximum VC value of less than 25 mL/kg during the first week of intubation. The risk of prolonged intubation (i.e., >2 wk) was 0% in patients with none of these risk factors, 20% in those with one risk factor, 50% in those with two, and 90% in those with three.[12] In another study, older age, baseline MG severity, number of comorbidities, pneumonia, and resuscitation history were factors associated with prolonged ventilation.[13] In MuSK antibody positive MG, there tends to be a longer need of intubation, ICU, and hospital stay.[90]

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Complications associated with a prolonged hospitalization for MC often include atelectasis, C *difficile* infection and other nosocomial infections, significant anemia, congestive heart failure, urinary tract infections, bacteremia, and sepsis. Prolonged immobility can also lead to deconditioning, and many MC patients are treated with steroids which puts them at risk for steroid myopathy. When compared to patients admitted for non-crisis, MG patients with MC are more likely to experience deep vein thrombosis, acute myocardial infarction, arrhythmias, and cardiac arrest.[8,14] *Clostridium difficile* enterocolitis, anemia requiring transfusion, and congestive heart failure represent complications independently associated with increased duration of MC.[12]

Recent data suggest that the mortality of MC in US hospital is approximately 4.5%, and the cause of death is primarily the result of comorbid conditions such as sepsis, cardiac arrest, multi-organ failure, or ARDS.[13,14] Data on mortality worldwide range between 2 to 16%. Predictors of mortality include age > 50 y, severe MG status, severe anemia, septic shock, cardiac arrest, number of comorbidities, ARDS and resuscitation need.[6,12–14,91,92] In a retrospective study of 5000 hospital admissions for MG, there were no deaths observed in those <40 y of age, highlighting the importance of age and medical comorbidities as modifying factors for the mortality of MC.[14]

Owing to better respiratory care and increased disease modifying treatment options, the prognosis of MC has improved strikingly over the last century. Many patients with MC can return to full productive lives with proper therapy. Duration of intubation is an important predictor of functional outcome after MC. In one series, 77% of patients intubated for more than 2 wk had functional dependence at discharge compared with 36% of patients intubated for less than 2 wk.[12]

Most patients who have had a crisis do not have a different prognosis or response to therapy than other patients with moderate to severe weakness. In patients admitted to the hospital with MG and dyspnea, those that progressed to crisis had similar long-term outcomes as those that did not, with half of patients being able to achieve minimal manifestations status subsequently.[93] Patients who survive MC can eventually have their MG controlled and even achieve remission. A small portion of patients may have recurrent MC.

A neuromuscular or neurology follow-up should be arranged at discharge for continued treatment adjustment. There is a need for ongoing management of tracheostomy by experienced pulmonary medicine or otolaryngology specialists for those patients who have received such a procedure. Involvement of physical and occupational therapists as well as dieticians and speech language pathologists both during and after MC can help identify skills that require rehabilitation. A neglected issue in the care of MC patients is the need for psychological support. It has been long recognized that sudden emotional stress may increase myasthenic weakness, and chronic weakness may influence the mental and emotional health of the affected individual.[94] Psychological support of a patient recovering from MC is no less important than medication therapy. Home-based inspiratory muscle training and breathing exercises are helpful for patients and may improve their respiratory muscle strength and endurance.[95]

AUTHOR CONTRIBUTIONS

Benjamin Claytor: Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. **Sung-Min Cho:** Data curation; formal analysis; writing – original draft. **Yuebing Li:** Conceptualization; data curation; formal analysis; supervision; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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